CHAPTER I

Introduction

Painful diseases of the locomoter system form one of the largest groups of diseases requiring medical treatment. The spectrum ranges from painful artritis, soft tissue rheumatism such as tendon and tendon shealth inflammations, periarthritis and inflammatory joint changes, to the large number of traumatic joints injuries such as sprains, strains and hematomas. (Chlud and Wagener, 1987). Diclofenac is one of the most potent non-steroidal anti-inflammatory agents which also exhibits anti-inflammatory, analgesic, and antipyretic activity. Systemic treatment of such diseases, i.e.oral,intramuscular, with diclofenac is very impressive. The drug is rapidly and efficiently absorbed after conventional oral or intramuscular administration. The side-effects, i.e. dyspepsia, gastrointestinal erosion and ulceration, from systemic treatment are usually dose dependent. They are closely related to the specific mechanism of action of drug. Diclofenac simultaneously inhibits prostaglandin synthesis and an important protective factor in the gastro-intestinal tract, so that gastro-intestinal adverse reactions are the most common one. Only a relatively small percentages of the side-effect adversed due to diclofenac are of an allergic type and thus, are normally unrelated to doses.

Localized use of diclofenac would show relative little risk, a good alternative to oral or parenteral therapy would be topical administration of drug.

Kohler et al.(1980) and Riess et al. (1986) reported that diclofenac which locally applied penetrated through skin into the target area, synovial fluid, with higher concentration than in plasma, while orally or intramuscularly administration showed the reverse. Parallel investigation of drug which locally applied showed that only very low concentrations occurred in the plasma and were unlikely to lead to systemic effects or side effects. But, it had been conclusively shown that the concentration of diclofenac in the synovial fluid reached the level necessary to achieve their therapeutic effect even when applied locally.

Many reports stated that topical diclofenac was absorbed through skin and effective in treatment. Nishihata et al. (1988) stated that plasma level of diclofenac sodium in rat and human increased after topical administration of drug. Kroll et al. (1989) studied the effectiveness of topical diclofenac diethylammonium in the treatment of patients with well-defined, acute sprains and tendonitis of ankle, shoulder, or elbow. The results of this study showed that diclofenac was effective and well tolerated in the treatment of selected acute sprain and tendonitis.

There are several problems in the development of diclofenac topical formulation. One prominent problem of a topical formulation of diclofenac in aqueous system is the low solubility of diclofenac (Adeyeye and Li, 1990). Another problems of a topical formulation of diclofenac are dosage form and vehicle selection. The release of drug from different dosage forms was reportedly varied. And as described by Ostrenga et al. (1971) about the formulation of vehicle for topical drugs, the efficacy of such dosage form is often dependent on the composition of the vehicle. Different drug derivatives and salts were also reported to affect the release of drug. Since diclofenac is available as two different salts, selection of the salts is also to be considered.

Objectives of this study.

On the basis of the afore mentioned rationale, the objectives of this research are, therefore, to

1. preformulation study of two diclofenac salts, sodium and diethylammonium : solubility and stability,
2. formulate diclofenac sodium and diclofenac diethylammonium topical preparations in different dosage forms: o/w cream, hydrophilic gel and oil-water gel,
3. investigate the effect of amount and composition of oil phase on physical appearance and in-vitro release study of diclofenac from oil in water cream preparation,
4. investigate the effect of amount and type of gelling agent on physical appearance and in-vitro release study of diclofenac from hydrophilic gel preparation,
5. investigate the effect of an amount and type of oil phase on physical appearance and in-vitro release study of diclofenac from oil-water gel preparation,
6. study the release of diclofenac sodium and diclofenac diethylammonium from various dosage forms and commercial products,
7. study the effect of diclofenac salts on physical appearance and in-vitro release study of diclofenac topical preparation.

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LITERATURE REVIEWS

1. Diclofenac

Diclofenac, a phenylacetic acid derivative, is a non steroidal anti-inflammatory agent (NSAIA). The drug is structurally related to meclofenamate sodium and mefenamic acid, but unlike these anthranilic acid (2-aminobenzoic acid) derivatives, diclofenac is a 2-aminobenzeneacetic acid derivative.

1.1 Physicochemical properties

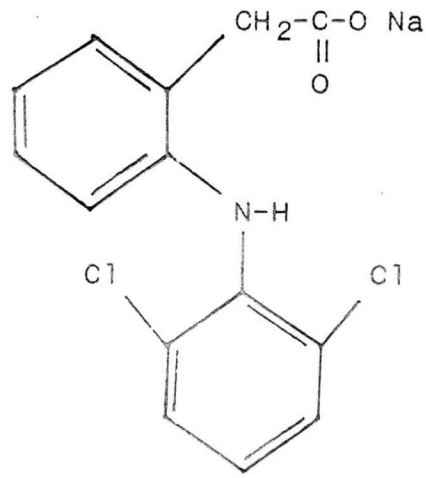
1.1.1 Diclofenac Sodium

Chemical name : 2-[(2,6-dichlorophenyl) amino] benzene acetic acid monosodium salts

Empirical formula : $C_{14}H_{10}Cl_2NNaO_2$

Molecular weight : 318.13

Structural formula :



Scheme : Diclofenac sodium

Description : Diclofenac sodium occurs as a faintly yellow to light beige, practically odorless, slightly hygroscopic crystalline powder and, at 25°C, has solubilities of 21 mg/mL in water at pH 7.68 and 75 mg/mL in alcohol. The pK_a of diclofenac sodium is approximately 4.

1.1.2 Diclofenac Diethylammonium

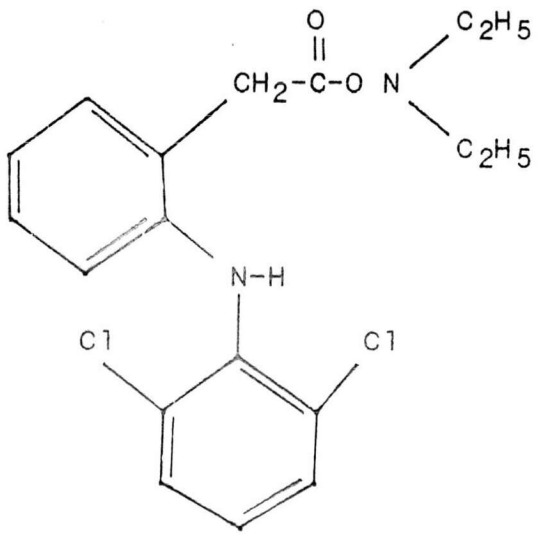
Common name : Diclofenac diethylammonium

Chemical name : 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid diethylammonium salts

Empirical formula : $C_{18}H_{22}Cl_2N_2O_2$

Molecular weight : 369.29

Structural formula :



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Scheme : Diclfenac Diethylammonium

Description : Diclofenac diethylammonium occurs as a white to beige crystalline powder. It is soluble in methanol, ethanol 96 % and chlorofrom.

1.2 Pharmacology

Diclofenac sodium has pharmacologic actions similar to those of other NSAIAs. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. The exact machanisms have not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Diclofenac may inhibit the synthesis of prostaglandin in body tissue by inhibiting cyclooxygenase, an enzyme that catalyzes the formation of prostaglandin precursors (endoperoxide) from arachidonic acid.

1.3 Pharmacokinetics

1.3.1 Absorption

Diclofenac sodium is rapidly and almost completely absorbed from the GI tract ; however, the drug undergoes extensive first-pass metabolism in the liver, with only about 50-60 % of a dose as enteric-coated tablets reaching systemic circulation as unchanged drug. Diclofenac is also absorbed into systemic circulation following rectal

administration and percutaneously following application to the skin as a gel.

1.3.2 Distribution

Distribution of diclofenac into human body tissue and fluids has not been fully characterized. Diclofenac is extensively but reversibly bound to plasma proteins, mainly albumin. At plasma diclofenac concentrations of 2-10 mcg/mL, the drug is 99-99.8 % protein bound in vitro.

1.3.3 Elimination

Following oral administration of enteric-coated diclofenac sodium tablets in healthy individuals or in patients with rheumatoid arthritis, the elimination half-life of the drug is approximately 1.2-2.0 hours.

1.4 Uses

Diclofenac is used for anti-inflammatory and analgesic effects in the symthomatic treatment of acute and chronic rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

1.5 Adverse effects

Adversed GI effects, which mainly involve the upper GI tract : peptic ulcer, GI bleeding, gastrointestinal erosion and ulceration, occur in about 20 % of patients receiving diclofenac.

1.6 Dosage and Administration

Diclofenac sodium is administered orally. For the symptomatic treatment of acute or chronic rheumatoid arthritis, the usual adult dosage of diclofenac sodium is 150-200 mg daily, administered in divided dose of 75 mg twice daily or 50 mg 3 or 4 times daily. For the sympatomatic treatment of oesteoarthritis, the usual adult dose of diclofenac sodium is 100-150 mg daily, administered in divided dose of 75 mg twice daily or 50 mg 2 or 3 times daily. For the treatment of ankylosing spondylitis, the usual adult dose of diclofenac sodium is 100-125 mg daily, administered in divideo dose of 25 mg 4 or 5 times daily. The drug also has been administered rectally, parenterally by IM injection and topically.

1.7 Commercial topical preparations

Dosanac ^{R} is a turbid gel product produced by Siam Pharmaceutical. It contained 1.16% of diclofenac diethylammonium equivalent to 1 % of diclofenac sodium.

Commercially available packagings are of 10 and 20 g.

Olfen ^{R} is a transparent gel produced by Mepha ,Amcron Enterprise. It contained 1 % of diclofenac sodium. Commercially available packagings are of 20 and 50 g.

Voltaren Emulgel ^{R} is a turbid gel product produced by Ciba Geigy. It contained 1.16% of diclofenac diethylammonium equivalent to 1 % of diclofenac sodium. Commercially available packagings are of 20 and 50 g.

2. Effect of drug derivative and components in dosage forms on the release study

There are many reports stated that amount of drug released from different bases and dosage form are unequal. And some paper reported that different derivatives and salts of drug affected the release from different dosage forms. From these different results, it is unable to conclude that which dosage forms and bases are good for drug. The best way for choosing an optimum dosage forms is preformulation and formulation in research and development state. These are some reports which supported the preveious conclusion.

Two derivatives of fluocinolone in propylene glycol-water gel were tested for their absorption by Poulsen et al. (1968). Fluocinolone acetonide released 70 % and 25 % from

propylene glycol-water gel which contained 20 % and 70 % of propylene glycol, respectively, whereas fluocinolone acetonide acetate conversely released 15 % and 45 % from the same respective gels.

Dexamethasone released from water soluble base and oil in water emulsion base more than from oleageneous, absorption or water in oil emulsion base. (Habib et al., 1989)

Babar et al. (1989) studied the in-vitro release of testosterone from various topical bases. The general rank order of testosterone released from these base was : water-washable base > hydrophilic base > University of California Hospital base > gel base > cream base > water soluble base > emulsion base.

Betamethasone-17-valerate released from water in oil cream > oil in water cream > ointment base. (Rekkas et al. ,1989)

Ezzedeen et al. (1990) had studied the release of cephalexin, sulfamethoxazole and diphenhydramine from various topical bases. The general rank order of released from these bases was : for cephalexin, oil in water emulsion base > water soluble base > hydrophilic base > oleageneous base > water in oil emulsion base, for sulphamethoxazole : water soluble base > oil in water

emulsion base > water in oil emulsion base = oleageneous base = hydrophilic base, for diphenhydramine : oil in water emulsion base > water soluble base > hydrophilic base > oleageneous base = water in oil emulsion base.

Rahman et al.(1990) had studied the in vitro release of naproxen from various topical bases. The general rank order of drug released was : modified University of California Hospital base > gel base > anhydrous ointment base.

Barbar et al. (1990) had been studied the in vitro release of piroxicam from various topical bases. The general rank order for the in vitro drug release from all the base evaluated was : gel base > hydrophilic base > emulsion base.

3. In vitro release study

In vitro release study of topical preparation is simplicity and economic advantage in formulation delvelopment and for optimizing of dosage form and vehicle compositions. There are many models of diffusion cell for in vitro release study of topical preparation. For the production, it is important to appreciate the need to control the experimental conditions or variable which can affect the apparent kinetics of penetration that may lead to errorneous in vivo prediction (Gummer, 1989). The major

variables which should be concerned in design characteristics of diffusion cell are temperature control and the condition of hydrodynamics, stirring rate, in the receptor compartment, because the rate of diffusion will increase with increasing temperature (Guy and Hadgraft,1985) In addition, the attention to human body temperature, the skin surface temperature (32 $\pm$ 1 ^{o}C) and the body core temperature (37 ^{o}C) are specified. As mentioned, the diffusion of drug in release study through dissolution medium may act as a rate-limiting step. Thus, good designation in optimum stirring pattern and rate can improve the flow pattern of medium solution, the hydrodynamics of medium solution and mixing efficiency which provide homogeity of drug.

3.1 Franz diffusion cell

Franz diffusion cell, finite-dosing upright type, one of the most frequently used in vitro techniques for skin or membrane permeation studies, was designed and developed by Franz. Schemic illustration of the commercially available Franz diffusion cell assembly is shown in Figure 1. Each of the diffusion cells in a cell mount block is consists of two compartments; a donor compartment, which is exposed to an ambient condition, and a receptor compartment which is maintained at 37 ^{o}C by circulating water through the water jacket. The solution hydrodynamics in the receptor compartment is kept at constant by a tiny rod-shaped

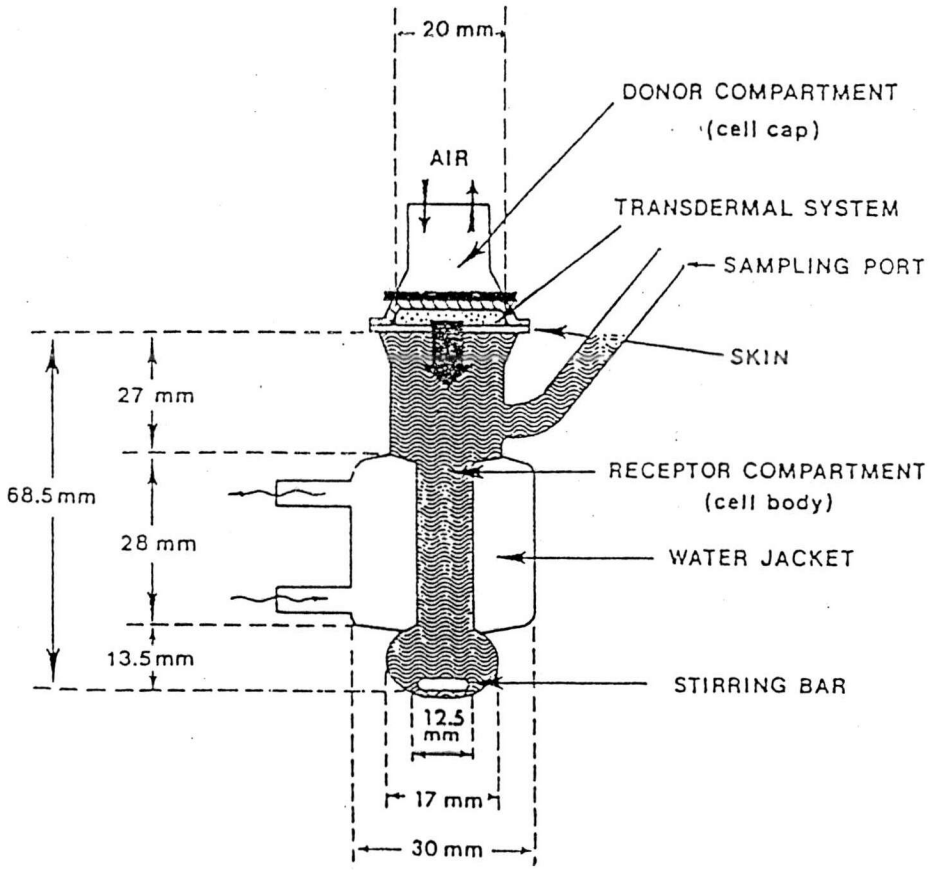

Figure 1 Schematic illustration of Franz-diffusion cell

magnet rotating at 600 rpm by a synchronous motor mounted underneath the cell mounting block. Nevertheless, there are several deficiencies in the Franz diffusion design. It is shown incomplete stirring of receptor phase that could not acheive the solution hydrodynamics, mixing efficiency. And it is sensitive to any variations in the atmospheric temperature that cause unconstant in temperature control.

3.2 Chien-Valia diffusion cell

Chien and Valia had designed the horizontal arrange diffusion cell with aiming to minimize the potential deficiencies observed in Franz diffusion cell. This cell call Chien-Valia side by side cell (Figure 2). It is composed of a skin permeation cell and a magnetic driving unit, which consists of two half cells in mirror image. Each of the half cells contains a solution chamber within a stirring platform to rotate at a synchonous speed. A sample port on solution chamber could be tightly closed with glass stopper. Chein and Valia suggested that their diffusion cell showed consistently superior than Franz diffusion cell, by comparative studies, in term of the control of skin surface temperature and the efficiency of solution mixing. This horizontal diffusion cell is capable of simultating a clinical setting by maintaining the receptor solution at body temperature, while varying the temperature on skin surface.

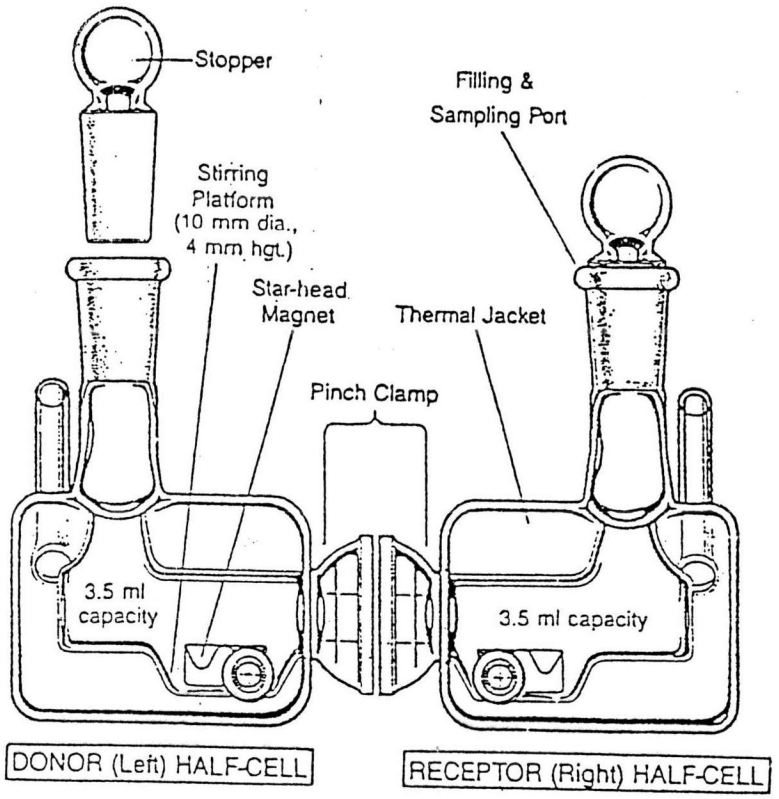

Figure 2 Schematic illustration of Chien-Valia diffusion cell

3.3 USP dissolution apparatus 3 : Paddle over disk (as shown in Figure 3)

The USP apparatus for release study of transdermal preparation is adapted from USP dissolution apparatus 2 using stainless steel disk instead of tablet or capsule. A stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel. The dissolution medium place into the vessel at the desired volume and the temperature is maintained at 32 ± 0.5 ^{o}C. The transdermal system is applied to the disk assembly, assuring that the release surface of the system is as flat as possible. If a membrane is used to support the system, it is applied so that no air bubbles occur between the membrane and the release surface. A distance of 25 + 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The paddle operate at the rate specified in the monograph. The vessel may be covered during the test to minimize evaporations. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.

3.4 A Jar with Semipermeable Membrane Method

This method is the simplest way to study the release of topical preparation. One-ounce plastic jars (Rahman et al., 1990)or two ounce jar of 2 inches diameter

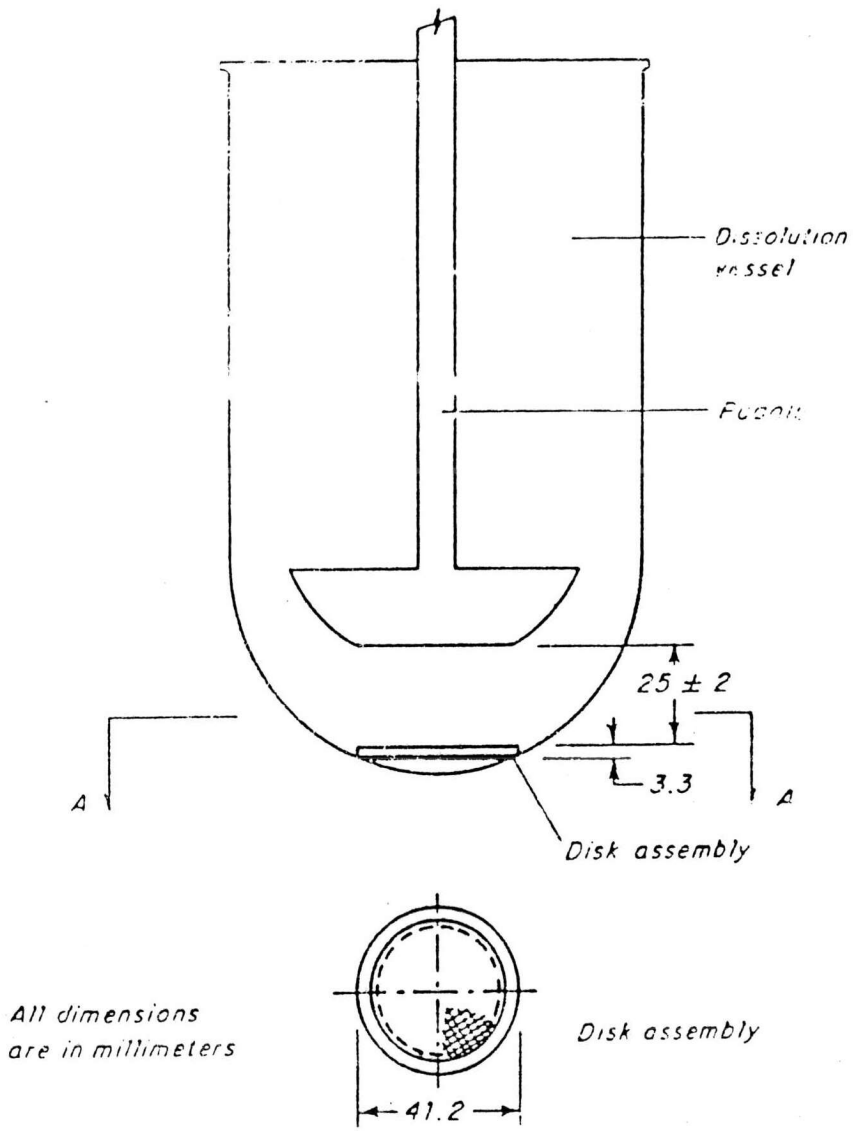

Figure 3 Schematic illustration of USP dissolution apparatus 3 : Paddle over Disk

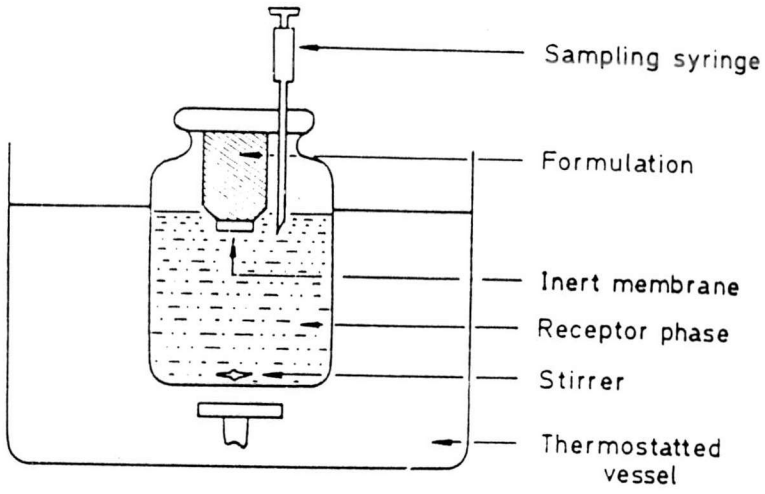

Figure 4 Schematic illustration of a Jar with semi-permeable membrane diffusion cell

with an approximate surface area of 3.4 square inches (Babar et al., 1989) is used for the in-vitro release studies of the drug.(Figure 4) The clean, pre-weighed jar is completely filled with the sample, and the excess of sample is removed from the surface with the edge of spatula to obtain an even and smooth surface. This is weighed again to determine the exact amount of sample employed in the experiment. The surhace of the sample is covered with a semipermeable membrane, and is secured with a silk thread. The jar is then inverted and immersed into 300-400 mL of diffusion medium, contained in a 600 mL beaker maintained at 37 $\pm$ 1 ^{o}C in a water bath. The diffudion medium is stirred constantly to prevent the development of any concentration gradient with in the medium.

3.5 Key Method (as shown in Figure 5)

This diffusion cell is composed of two 7 centimeters circular plastic plates with an 8 square centimeters in the top disc. The preparation sample with membrane is placed between the plates with the membrane side of the sample facing the opening. The plates are held together by stainless steel screws, and the assembly is place at the bottom of the dissolution vessel with the opening in the holder facing up. The same apparatus as used in the FDA and the USP method with a paddle speed of 100 rpm and a dissolution medium temperature 37 $\pm$ 0.5 ^{o}C. Other size diffusion cell are used for other size sample

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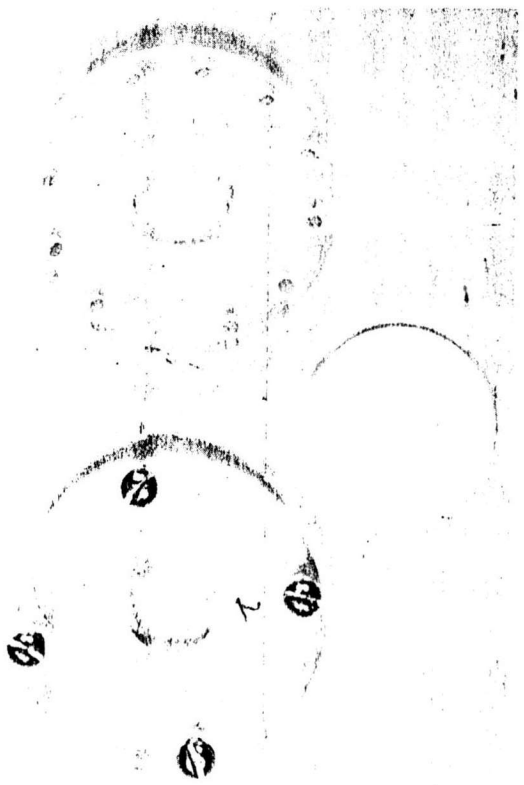

Figure 5 Schematic illustration of diffusion cell of Key Method

with membranes. (Shah et al., 1988)

3.6 Searle Method (as shown in Figure 6)

A stainless steel circular disc , 5.6 centimeters diameter, over which fits a stainless steel screw cap with an 8 square centimeters opening. The disc is attached to a 3/8 inch diameter stainless steel rod. The preparation sample with the membrane is trimmed to fit the stainless steel holder, with the membrane facing the opening. A holder with a 4 square centimeters opening is used for a smaller membrane from Searle. The same apparatus as used in the USP method except the stainless steel holder replace the paddle and 300 mL water at 37 $\pm$ 0.5 ^{o}C is used for the dissolution medium (Shah et al., 1988)

3.7 Polano and Ponac Diffusion Cell

A polycarbonate diffusion cell is constructed according to the model of Polano and Ponac (Provost et al., 1989). (Figure 7) The cell consists of three parts assembled by mean of wings and nuts. The lower part of the cell contains a 0.78 cubic centimeter acceptor compartment(part A) provided with a sampling port. The second part, holding the donor compartment B, is closed by means of the top cover C. The effective diffusion area amounts to 0.78 square centimeters. The membrane are mounted in the diffusion cells and the acceptor compartment is filled with 0.75 mL of

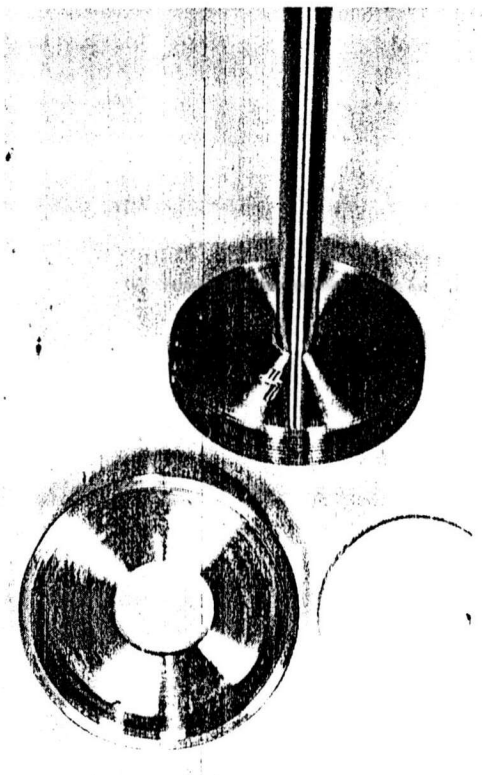

Figure 6 Schematic illustration of diffusion cell of Searle Method

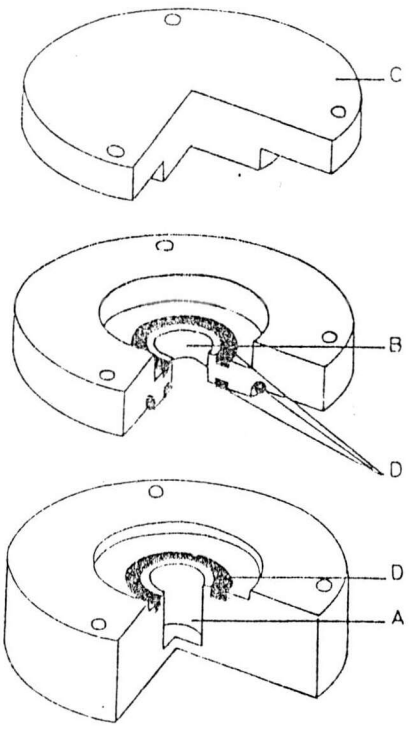

FIGURE 1

Diffusion cell used in the penetration experiment:
A. Acceptor compartment
B. Donor compartment
C. Top cover
D. Rubber sealing ring

Figure 7 Schematic illustration of Polano and Ponac diffusion cell

physiological saline. The sample are applied to the membrane using the finite dose technique and the cells are closed. Throughout the experiment the cell are kept at a temperature of 32 ^{o}C and agitated. At selected time intervals the acceptor fluid is completely removed through the sampling port and replaced with 0.75 mL of fresh acceptor fluid thus ensuring "sink" conditions.

3.8 Enhancer Cell

Enhancer cell, a new device for in vitro topical drug diffusion testing, is recently developed by Vankel Industries, Inc (Sanghvi and Collins, 1993). It consisted of a metal load ring, a cap, a washer, a membrane, an O-ring, and a drug resevoir comprising of a body and a screw. The sample is placed in the drug resevoir. A circular piece of cellulose membrane, 3 centimeters in diameter, is placed on the top of the drug resevoir followed by the washer as shown in Figure 8 . The metal load ring is removed. Finally, the bottom screw is tightened to bring the sample in complete contact with the membrane making certain that no entrapped air is present at the interface of the sample and membrane. A USP dissolution tedter ias used for evaluation of the enhancer cell. The flask assembly is modified (Figure 9) because 200 mL capacity flasks are used instead of the standard 900 mL flasks. The flask centering ring assembly modification differed from the standard flask assembly in that it

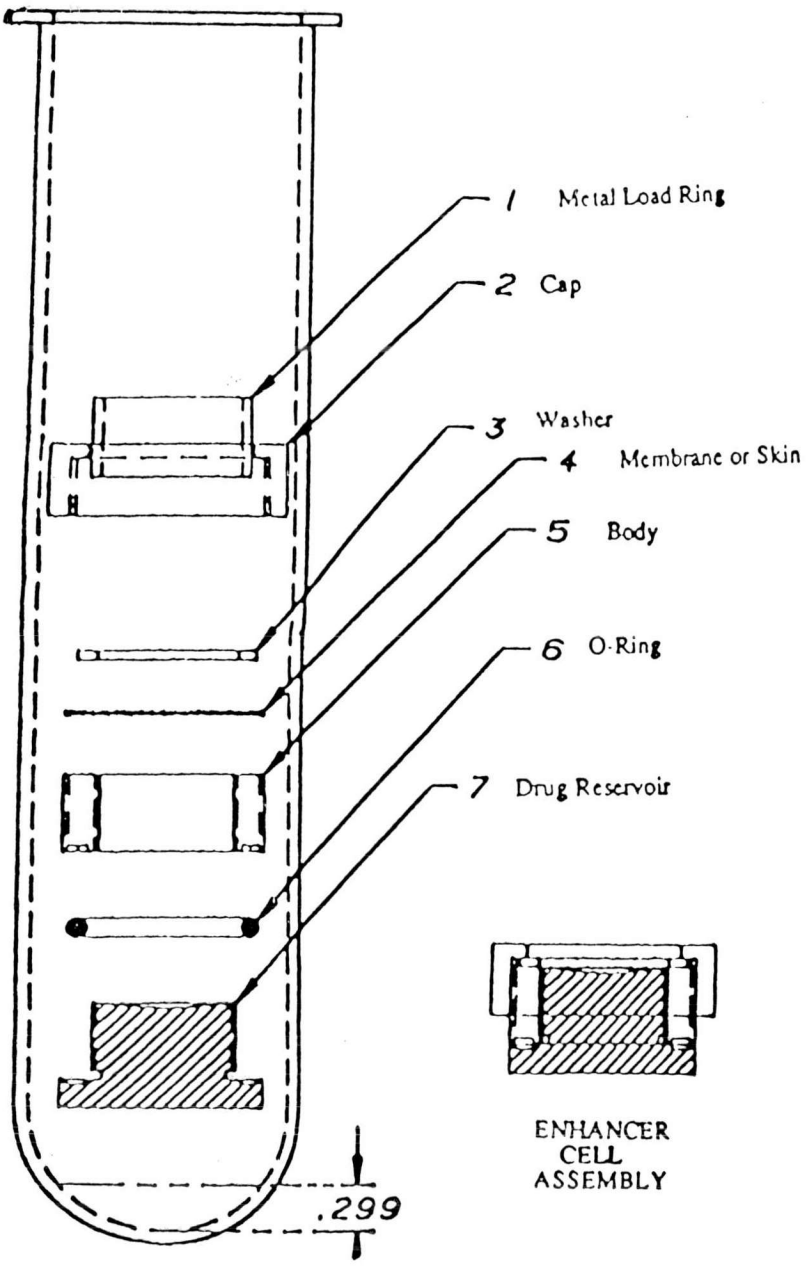

Figure 8 Schematic Diagram of Enhancer Cell

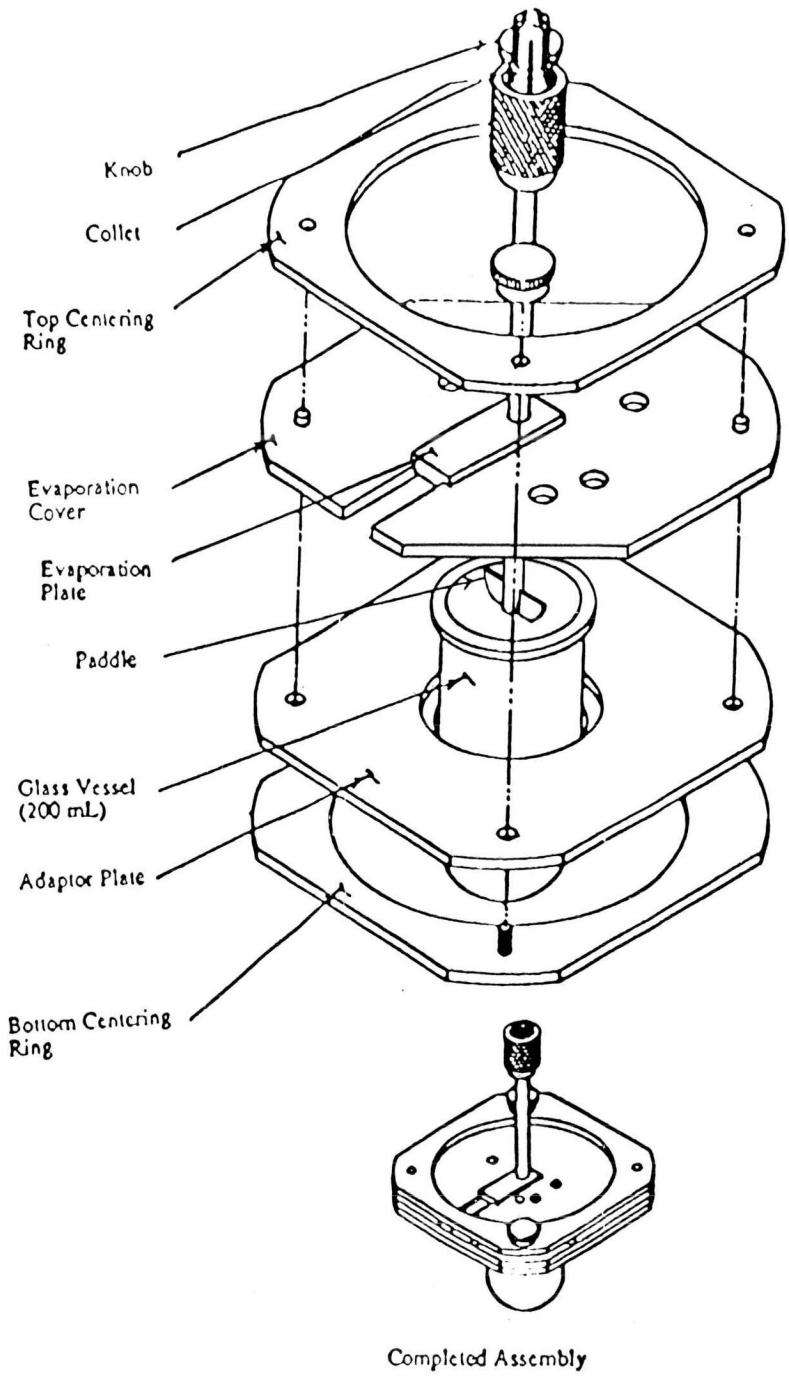

Figure 9 Schematic Diagram of 200 mL Flask Centering Ring Assembly

included an additional adapter plate to hold the smaller sized 200 mL flask inthe center, an evaporation plate that fits on the evaporation cover such that together they cover the flask completely at the top, smaller sized paddles (1/4 inch shaft) and 1/4 inch collets to fit the paddles. Water is used as the receptor phase medium. The enhancer cell including the sample is placed into the dissolution flask. The flask assembly is then completed, the receptor phase medium (200 mL) is poured into the flask, and the paddles rotated at 100 rpm.

4. Base's material

(American Pharmaceutical Association and the Pharmaceutical Society of Great Britain., 1986)

There are many dosage froms preparing for topical use. The preferable of those are semisolid dosage form including cream and gel. A viscous emulsion is also used for topical. Emusion is one of dosage forms composed of liquid oil phase, emulsifier and aqueous phase. Creams are semisolid emulsions containing all ingredients the same as emulsion and solid oil phase or wax. (Ansel, 1981) Gel are defined as semisolid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by a liquid. There are many gelling agent used in gel preparations. Most natural gums, such as acacia, carrageenan, and xanthan gum, are anionic polysaccharides. A number of cellulose

derivatives have been synthesized and are effective gellants; among them are sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and methylhydroxypropyl cellulose. Polypeptides (gelatin) and synthetics block copolymers, like poloxamer, are two additional chemical gelling agents. (Zatz et al., 1989)

There are many material that used in diclofenac topical preparation. These materials are affected both the physical appearance of preparation and the release of drug from bases as the previous mentioned.

4.1 Poloxamer 407

Poloxamer 407 is polyethylene polypropylene glycol block copolymer which is white, waxy, free-flowing prilled granules or cast solid, practically tasteless and odorless. It is soluble in water, diluted acid and ethyl alcohol but insoluble in propylene glycol, glycerin, mineral oil and liquid paraffin. It is very slightly hygroscopic and use as wetting, solubilizing, emulsifying, foaming and gel-forming agent.

Chen-Chow and Frank (1981) studied the in-vitro release of lidocaine from Pluronic F-127 gel using a membranless apparatus. It was reported that the release rate of the drug was inversely propotional to the concentration of Pluronic F-127. The drug was release by diffusion

through the extramicellar aqueous channels of the gel matrix.

Pluronic F-127 was used in sustained release depot formulation by Hadgraft and Howard (1982). Their results were similar to Chen-Chow and Frank. The increasing concentration of Pluronic F-127 in the vehicle made a corresponding decrease in apparent diffusion coefficient of the drugs. They suggested that the machanism for reduce release rate might be due to the reduction size and number of water channels within the gel matrix.

Fults and Jhonston (1990) studied the potential of poloxamer 407 as a sustained release vehicle for urease enzyme, polypeptide drug. The release of protein from the gel matrices was relately constant, zero-order, over 8 hours. The suggested that a protein drugs in poloxamer gel might be more stable.

4.2 Carbomer

Carbomer is a synonym of carboxypolymethylene, carboxy vinyl polymer, acrylic acid polymer and carbopol. It occurs as a white, fluffy, acidic, hygropic powder with a slight characteristic odor. Carbomer is soluble in water, alcohol and glycerin. The pH of 1 % dispersion of carbomer in water is approximately 3.0. Carbomer is soluble in water, alcohol and glycerin. Agent that can neutralize carbomer include sodium hydroxide, potassium hydroxide, sodium

bicarbonate, borax, amino acids, polar organic amines such as triethanolamine, and lauryl and stearyl amines, which are used as gelling agents in nonpolar systems. One gram of carbomer is neutralized by approximately 400 mg of sodium hydroxide. Neutralized aqueous gels of carbomer are more viscous between pH 6 and pH 11. The viscosity is considerably reduced if the pH is <3 or >12. The viscosity is also reduced in the presence of strong electrolytes. Gels rapidly lose viscosity on expose to sunlight, but this reaction can be minimized by the addition of an antioxidant. Carbomer is hygroscopic. Carbomer is incompatible with phenol, cationic polymers strong acids and high concentration of electrolytes, and it discolored by resorcinol. Carbomer is used as emulsifying, suspending and gelling agent.

Gel-formulationd containing a nonsteroidal antinflammatory drug, tolmetin, were prepared using three different carbomers namely, carbopol 934, 940 and 941 (Macedo et al., 1993). No significant differences in drug release characteristics were observed between the three carbomer gels. Increasing the carbomer concentration from 1% w/w to 2% w/w had no significant eddect on drug release from gel formulations prepared with all the three different types of carbomers.

4.3 Carboxymethylcellulose Sodium

Carboxymethylcellulose sodium is sodium CMC or sodium cellulose glycolate or carmellose sodium. It is a cellulose derivative which is white to faintly yellow, odorless, hygroscopic powder or granular material having a faint paper-like taste. It is soluble in water at all temperature, giving a clear solution; practically insoluble in most organic solvents. Aqueous solution of sodium CMC exhibit pseudoplastic flow behavier. Carboxymethylcellulose sodium is incompatible with strongly acidic solution and with soluble salts of iron and some other metals, such as aluminium, mercury, and zinc. Sodium CMC is used as suspending and/or viscosity-increasing agent, tablet binder, coating agent, disintregrant, thickener and suspension stabilizer.

4.4 Polyoxyethylene Castor Oil Derivatives

Polyoxyethylene hydrogenated castor oil is glycerol polyethyleneglycol oxystearate, PEG 40 hydrogenated castoroil, polyoxyl 40 hydrogenated castor oil or cremophor RH 40. It is a white powder at rooom temperature. The odor is very faint and characteristic. It has a slight taste in aqueous solution. Cremophor RH 40' s HLB value is 14-16. Cremophor RH can soluble in water which the solubility decreases with a rise in temperature, ethanol, propan-1-ol, and propan-2-ol. They can miscible on heating with fatty

acid (e.g. oleic and stearic), fatty alcohol (e.g. lauryl and stearyl) and some oils of animal and vegetable origin (e.g. castor oil and olive oil). It uses as wetting and/or solubilizing agent, nonionic emulsifying and/or solubilizing agent and dispersing agent.

An one ml of a 25 % solution of cremophor RH 40 is possible to solubilize: appoximately 88 mg of vitamin A palmitate or 160 mg of vitamin A propionate. In aerosol vehicles which include water, the addition of cremophor RH 40 improves the solubility of the propellant in the aqueous phase.

Cremophor RH 40 was used as a solubilising agent of nystatin, water insoluble drug, in chewing gum preparation (Andersen et al., 1990). Ading a solubilising agent to chewing gum containing nystatin cause a surprisingly drastic increase in the release of nystatin. Cremophor RH 40 show a 50 times increase.